$$\log (1/C_{50}) = 0.361\pi - 0.281R + 4.557 \quad (7)$$

of log $(1/C_{50})$ agree to a mean value of ± 0.102. Again the relation corresponds closely to our analysis of antagonism toward acetylcholine. A better study of antagonism toward histamine could be made with more satisfactory and specific antagonists.

Acknowledgments.—One of us (R. C. T.) is indebted to the Medical Research Council for a Research Scholarship.

Antimalarials. 8-Chloro-4-(2′-*N*,*N*-dibutylamino-1′-hydroxyethyl)benzo[*h*]-1,6-naphthyridine[1a]

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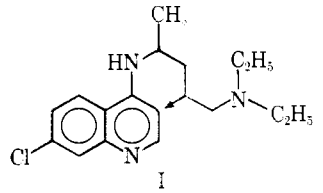
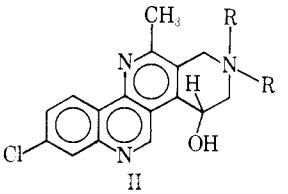
8-Chloro-4-(2′-*N*,*N*-dibutylamino-1′-hydroxyethyl)benzo[*h*]-1,6-naphthyridine (**17**) was synthesized from 4-amino-7-chloroquinoline. While a number of electrophiles failed to react with the weakly nucleophilic 4-amino function of the 4-aminoquinoline, utilization of diethyl ethoxymethylenemalonate, a relatively strong electrophile, provided a route to the tricyclic heteroaromatic compound. Whereas eight of its intermediates lacked antimalarial activity, 8-chloro-4-(2′-*N*,*N*-dibutylamino-1′-hydroxyethyl)benzo[*h*]-1,6-naphthyridine was active against *Plasmodium berghei* in mice. This compound, however, possessed only slight activity against *P. gallinaceum* in chicks and was ineffective against this organism in mosquitoes.

Initially, it was our desire to prepare 2-methyl-4-(*N*,*N*-dialkylaminomethyl)benzo[*h*]-1,6-naphthyridines. The nucleus and general substitution pattern of this molecule are derived by the "paper cyclization" of the chloroquine (I) side chain (as indicated by the arrow), along with aromatization of the formed third ring.



I



II

Consideration of the antimalarial activity found in the 4-quinolinemethanol series as well as in that of the phenanthrenemethanols[2,3] led to the refinement of replacing the formed dialkylaminomethyl group by a 2′-dialkylamino-1′-hydroxyethyl species at the 4 position of the benzo[*h*]-1,6-naphthyridine (II).

Synthesis of the candidate antimalarial required the presence of a usable functional group at the 4-position of the tricyclic heteroaromatic nucleus. Since a benzo[*h*]-1,6-naphthyridin-4-ol (**9**) possessed a requisite functionality, we sought a reaction which would provide this type intermediate in high yields. The acid-catalyzed Conrad–Limpach reaction between 4-aminoquinoline and acetoacetic ester has been reported to give high yields of 2-methylbenzo[*h*]-1,6-naphthyridin-4-ol.[4] Applying this procedure,[4] we were unable to isolate the desired benzo[*h*]-1,6-naphthyridin-4-ols or their possible quinolylcrotonate intermediates from the reactions of 4-aminoquinoline or 4-amino-7-chloroquinoline with acetoacetic or benzoylacetic esters. Similarly, these reactants did not provide the quinolylaminocrotonates under conditions which normally yield anilinocrotonates from anilines and acetoacetic ester.[5] The Doebner[6] and Niementowsky[7] reactions were equally ineffective in providing desired benzo[*h*]-1,6-naphthyridines from 4-aminoquinolines and ethyl 4-amino-7-chloroquinoline-3-carboxylate, respectively.

Although the quinolylaminocrotonate (**3**) was not obtained upon treatment of 4-amino-7-chloroquinoline (**5**) with ethyl β-ethoxy-*cis*-crotonate, somewhat encouraging results were obtained when 4,7-dichloroquinoline (**1**) was treated with ethyl 3-aminocrotonate (**2**) to give the crotonate in 20–30% yields. All attempts to obtain the benzo[*h*]-1,6-naphthyridin-4-ol by cyclization of **3** were unsuccessful.

In a manner similar to the EMME synthesis[8] of quinolines and benzo[*h*]-1,6-naphthyridines,[4,9] we prepared 8-chlorobenzo[*h*]-1,6-naphthyridin-4-ol (**9**) from diethyl ethoxymethylenemalonate (EMME) and 4-amino-7-chloroquinoline (**5**) according to Scheme I. This intermediate did not possess the desired ring substitution at the 2-position. Bromination of 8-chlorobenzo[*h*]-1,6-naphthyridin-4-ol (**9**) yielded the bromo derivative (**10**) which was treated with CuCN to give the 4-cyano compound **11** (Scheme II). A small amount of DMSO was required to effect the aqueous alkaline hydrolysis of this nitrile to the acid **12**. The overall yield of the recrystallized acid (Table I) was 26%. The final product (**17**) was prepared from this acid using the general synthetic pathway of Lutz, *et al.*,[10] where similar quinolinemethanols were prepared.

(1) (a) The work described in this paper was performed under Contract No. DADA17-67-C-7060 with the U. S. Army Medical Research and Development Command. This is Contribution No. 665 from the Army Research Program on malaria. (b) To whom inquiries should be addressed.

(2) F. Y. Wiselogle, Ed. "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.

(3) G. R. Coatney, "Survey of Antimalarial Agents," Public Health Service Monograph No. 9, Federal Security Agency, 1952.

(4) C. R. Hauser and G. A. Reynolds, *J. Org. Chem.*, **15**, 1224 (1950).

(5) G. A. Reynolds and C. R. Hauser, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, New York, N. Y., 1955, p 374.

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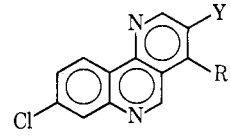
(7) R. C. Fuson and D. M. Burness, *ibid.*, **68**, 1270 (1946).

(8) C. C. Price and R. M. Roberts, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, New York, N. Y., 1955, p 272.

(9) M. Davis, *J. Chem. Soc.*, 828 (1958).

(10) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).

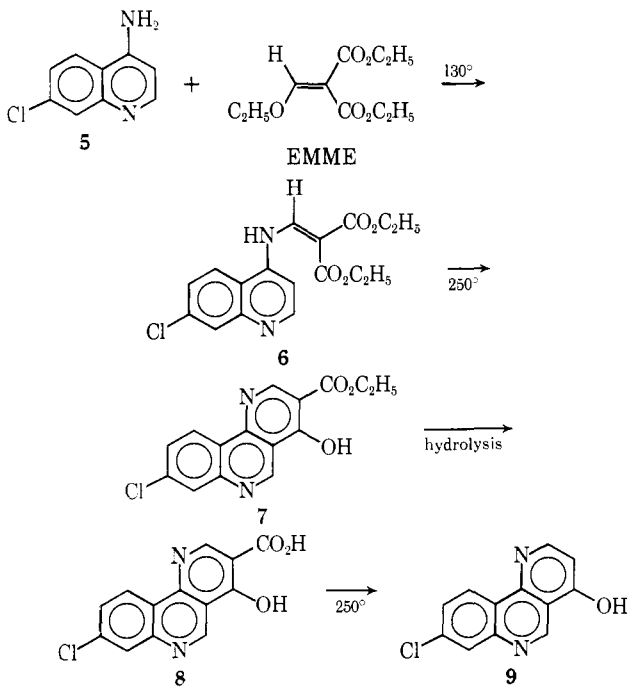
TABLE I
8-CHLOROBENZO[h]-1,6-NAPHTHYRIDINES



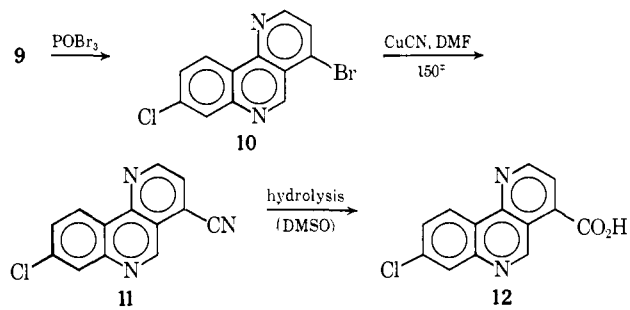
No.	R	Y	Mp, °C	Crystln solvent	% Yield	Formula	Analyses[a]
7	OH	$CO_2C_2H_5$	307–308[b]	DMF	95[c]	$C_{15}H_{11}ClN_2O_3$	C, H, Cl, N
8	OH	CO_2H	*d*	DMF	88[e]	$C_{13}H_7ClN_2O_3$	C, H, Cl, N
9	OH	H	*f*	DMF–EtOH	81[e]	$C_{12}H_7ClN_2O$	C, H, Cl, N
10	Br	H	155–157	Petr ether–601–10	74[g]	$C_{12}H_6ClBrN_2$	C, H, Br, Cl, N
11	CN	H	258–259	EtOAc	78[g]	$C_{13}H_6ClN_3$	C, H, Cl, N
12	CO_2H	H	324[b]	DMF–EtOH	67[g]	$C_{13}H_7ClN_2O_2$	C, H, Cl, N
13	COCl	H	182–187		96[e]		
14	$COCHN_2$	H	*h*				
15	$COCH_2Br$	H	154[b]	Cyclohexane	75[e]	$C_{14}H_8BrClN_2O$	C, H, Br, Cl, N
16		H	186–188[b]	EtOAc	97[e]		
17	$CHOHCH_2N(C_4H_9)_2$	H	90–91	MeOH–H_2O	67[i]	$C_{22}H_{28}ClN_3O$	C, H, Cl, N

[a] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [b] Melt with decomposition. [c] Yield of washed product based upon the amount of 4-amino-7-chloroquinoline. [d] Sample charred at 310°, no melt below 360°. [e] Yield of washed product. [f] Charred at 360°, no melt. [g] Yield of recrystallized product. [h] Explosive decomposition above 187°. [i] Yield of crude product based on the amount of bromomethyl ketone (**15**).

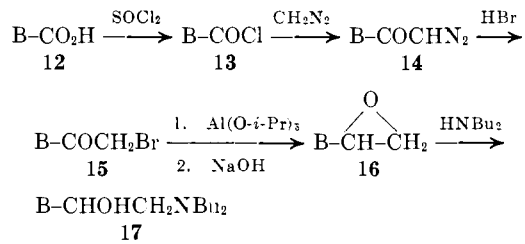
SCHEME I



SCHEME II



SCHEME III



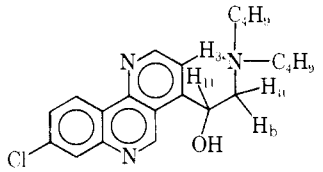
B = 4-(8-chlorobenzo[*h*]-1,6-naphthyridyl)

In contrast to the reduction of some quinolyl bromomethyl ketones in which $NaBH_4$ *or* $Al(O\text{-}i\text{-}Pr)_3$[11] can be used to reduce the ketone function, only $Al(O\text{-}i\text{-}Pr)_3$ was of value since $NaBH_4$ gave concurrent partial reduction of the tricyclic, heteroaromatic ring system when used in an equimolar concentration at 5°. The crude bromohydrin product of the Meerwein–Ponndorf–Verley reduction was treated with base to yield the oxirane (**16**) as given in Scheme III. This in turn was treated with *n*-Bu_2NH to prepare **17**, the final product. It has been shown that this type of oxide is equivalent to the bromohydrin in the subsequent reaction with amines.[12]

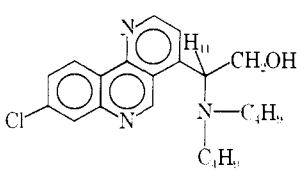
(11) R. C. Elderfield, M. Israel, J. H. Ross, and J. A. Waters, *J. Org. Chem.*, **26**, 2827 (1961).
(12) S. Winstein, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1831 (1946).

The pmr spectra for intermediates **6**, **10**, **11**, **14**, **15**, and **16** were consistent with the assigned structures and with the expected changes within the series of spectra which includes the starting material and final product. Compounds **7**, **8**, **9**, **12**, and **13** were not sufficiently soluble in pmr solvents to permit recording of their spectra. Thus, the pmr spectrum of the ring closure product of the acrylate, **6**, showed the loss of the 3-quinoline proton with concurrent collapse of the number 2 proton doublet to a singlet. Analysis of the pmr spectra not only allowed for assignment of *all* signals in the pmr spectra but also yielded the coupling constants. The doublet of the aromatic number 3 proton of the oxirane, **16**, showed an additional splitting of 0.7 Hz which is attributed to long-range coupling with the ethylene oxide methine proton. The methine signals were broad but the corresponding 0.7-Hz splitting could

not be resolved. This long-range coupling is also observed in the spectrum of the final product. Pmr data clearly show that the product isolated is **17** and not the alternate isomer **18** which could be obtained from the reaction of the epoxide (**16**) with dibutylamine.



17



18

In the case of the alternate isomer, **18**, the methylenehydroxy protons ($-CH_2OH$) should appear in the region of 240 Hz (TMS) with AB pattern characteristics. (Since this group is adjacent to an asymmetric center, these geminal protons are not expected to be equivalent.) Furthermore this group should integrate to 2 protons. This was not the case. A multiplet at 331 Hz, integrating to one proton, was readily assigned as H_n of **17**, while protons a and b appeared with the other aminomethylene (NCH_2) signals.

Biological Activity.—Eight intermediates and the 8-chloro-4-(2′-*N*,*N*-dibutylamino-1′-hydroxyethyl)benzo[*h*]-1,6-naphthyridine were tested for antimalarial activity. The results of these tests were furnished to us by the Walter Reed Army Institute of Research. Intermediates **6**, **8**, **9**, **10**, **11**, **12**, and **15** were tested against *P. gallinaceum* in mosquitoes,[13] and were inactive in this test. The bromomethyl ketone, **15**, yielded a 50% oocyst suppression which was not significant since there was no corresponding sporozoite suppression. Similarly **6**, **7**, **8**, **10**, **11**, and **12** showed no activity when tested against *P. berghei* in mice[14] in a dosage range of 40 to 640 mg/kg given in single subcutaneous doses.

8-Chloro-4-(2′-*N*,*N*-dibutylamino-1′-hydroxyethyl)-benzo[*h*]-1,6-naphthyridine (**17**) was active against *P. berghei* in mice, extending the mean survival time to 6.9 days at a dosage of 640 mg/kg. Comparable data for the highly active 7-chloro-2-(*p*-chlorophenyl)-α-dibutylaminomethyl-4-quinolinemethanol[15] illustrate the disappointing activity of **17**; at a dosage of 640 mg/kg, the 2-substituted quinolinemethanol effects 4 cures (with 1 toxic death) while only a 20 mg/kg dose is sufficient to extend the mean survival time by 5.8 days. On the other hand, quinine sulfate shows a mean survival time extension of only 7.1 days at the upper level of 640 mg/kg. Compound **17** possessed no significant activity against *P. gallinaceum* in chicks and was inactive against this organism in mosquitoes.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are corrected to melting point standards. All compounds were characterized by their pmr and/or ir spectra as well as their elemental analyses and simple chemical behavior. Elemental analyses were performed by Dr. Kurt Eder, Laboratoire Microchimique, Ecole de Chimie, Geneve, Switzerland. Ir spectra (in KBr) were recorded on a Perkin-Elmer Model 21 spectrophotometer while pmr spectra (in $CDCl_3$) were obtained on a Varian Model A-60 spectrometer (Me_4Si; J in Hz).

4,7-Dichloroquinoline was commercially available[16] and was purified by recrystallization from Skellysolve B, mp 82–84.5° (lit.[17] mp 84–85°). The procedure for the preparation of intermediates **6** through **9** follows that of the EMME synthesis of quinolines,[5] while **13** through **17** were prepared according to the procedure of Lutz, *et al.*[18]

4-Amino-7-chloroquinoline (5). 4,7-Dichloroquinoline (20 g, 0.1 mol) was dissolved in PhOH and treated with anhydrous NH_3 according to the procedure of Elderfield, *et al.*[17] The thoroughly washed and dried crude product was recrystallized from C_6H_6 to yield 13.5 g (75%) of crystalline **5**: mp 152–154.4° (lit.[17] mp 150–151°).

Ethyl 2-Carbethoxy-3-(7-chloro-4-quinolylamino)acrylate (6).—A mixture of 45 g of 4-amino-7-chloroquinoline (**5**) and 60 ml of EMME was heated for 1 hr at 120–130° with stirring while allowing the formed EtOH to boil off. The analytical sample was recrystallized from petroleum ether (bp 60–110°) with refrigeration: mp 115.5–116.5°; ir and nmr as expected. *Anal.* ($C_{17}H_{19}ClNO_4$) C, H, Cl, N.

Ethyl 8-Chloro-4-hydroxybenzo[*h*]-1,6-naphthyridine-3-carboxylate (7).—The crude, molten acrylate **6** was carefully poured into 1600 ml of vigorously refluxing Dowtherm A[16] and allowed to reflux for 5 min. After cooling the mixture to room temperature the solid was filtered and boiled with two 400-ml portions of EtOH and one 300-ml portion of petroleum ether (bp 60–110°) to obtain 71.9 g (95%, 2 steps) of crude, air-dried product, mp 290–291° dec. An analytical sample, which required washing with Et_2O and drying at 100°, was obtained by recrystallization from DMF: mp 307.5–308.5° dec; ir as expected.

8-Chloro-4-hydroxybenzo[*h*]-1,6-naphthyridine-3-carboxylic Acid (8). The crude ester, **7**, was hydrolyzed by refluxing in 940 ml of 2.5% aqueous NaOH. After 2 hr of reflux, the reaction mixture was diluted with 1600 ml of H_2O, cooled, and filtered, first through a coarse porosity sintered funnel then through one of medium porosity. The clear, yellow filtrate was further diluted with 8700 ml of H_2O and acidified to a pH of 2 (pHydrion paper) using concentrated HCl (400 ml). After filtering and drying to constant weight (125°, 10 hr), 58.2 g (84%, 2 steps) of acid was obtained, mp 300°. The analytical sample (DMF) charred at 310° but did not melt; ir as expected.

8-Chlorobenzo[*h*]-1,6-naphthyridin-4-ol (9).—The crude acid, **8**, was carefully added to 2100 ml of vigorously refluxing Dowtherm A[16] and after 2 hr of heating, the dark reaction mixture was cooled and the brown decarboxylation product was filtered. The solid was boiled with two 400-ml portions of EtOH and 500 ml of petroleum ether (bp 65–110°) to yield 39.7 g (68%, 4 steps) of crude **9** after air drying. The analytical sample, recrystallized from DMF–EtOH, charred at 360° but did not melt; ir as expected.

4-Bromo-8-chlorobenzo[*h*]-1,6-naphthyridine (10). A solution of 54 g of $POBr_3$ in 180 ml of $CHCl_3$ was added to a mixture of 39 g of **9** in 100 ml of $CHCl_3$ with stirring. The mixture was heated at reflux for 4 hr, cooled, and filtered. The collected solid was mixed with 300 ml of H_2O and the mixture was neutralized to pH 7 using 5% $NaHCO_3$ solution. After filtering and drying the solid *in vacuo* over H_2SO_4 (14 mm), the product was extracted with 1600 ml of boiling petroleum ether (bp 60–110°) which deposited 28.2 g of fluffy white needles upon refrigeration. The residual solid was then extracted with the petroleum ether filtrate of crystallization and deposited an additional 8.8 g of product after concentration to 500 ml and refrigeration. The 37 g total, mp 156.5–159.5°, represented an overall five-step yield of 50%. The analytical sample from petroleum ether (bp 60–110°) melted at 155.5–157.5°; ir and nmr as expected.

8-Chloro-4-cyanobenzo[*h*]-1,6-naphthyridine (11).—A mixture of 300 ml of DMF (bp 152.5–153.1°), 18 g (0.006 mol) of **10**, and 12 g of CuCN (CP) was purged with dry N_2 and the mixture was heated at reflux for 5.5 hr with stirring while maintaining a positive N_2 pressure. After 20 min of reflux, the solid dissolved. An additional 30 min of heating produced a copious amount of

(13) E. J. Gerberg, L. T. Richards, and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

(14) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(15) SN 13,710—Wiselogle, "Survey of Antimalarial Drugs," Vol. II, J. W. Edwards, Ann Arbor, Mich., 1946, p 1084. Specific data for SN 13,710 and quinine sulfate was supplied by the Walter Reed Army Institute of Research.

(16) Winthrop Laboratories, Special Chemicals Dept.

(17) R. C. Elderfield, W. J. Gensler, O. Birstein, F. J. Kreysa, J. F. Maynard, and J. Galbreath, *J. Amer. Chem. Soc.*, **68**, 1250 (1946).

solid which gradually diminished upon continued reflux. The cooled, orange, semisolid reaction mixture was stirred vigorously while adding 600 ml of 10% aqueous NaCN. After an additional 200 ml of H_2O was added, the mixture was stirred vigorously until creamy white. The white solid was filtered, washed thoroughly with 500 ml of H_2O, and dried *in vacuo* (10 Torr) over H_2SO_4. One recrystallization of the product from EtOAc provided 10 g of cream colored crystalline solid, mp 255–258.5°. Concentration of the recrystallization filtrate yielded an additional 1.4 g of solid, mp 242–252° (78% total yield). The white, fluffy crystals of the analytical sample melted at 258–259°; ir and nmr as expected.

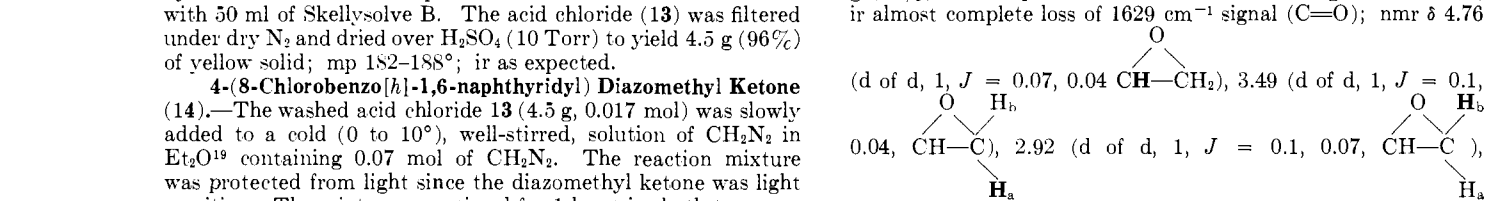
8-Chlorobenzo[*h*]-1,6-naphthyridine-4-carboxylic Acid (12).—Nitrile **11** (11.4 g) was hydrolyzed by a solution containing 5.7 g of NaOH and 1.5 ml of DMSO in 100 ml of H_2O. DMSO was required since the intermediate was not wetted by aqueous NaOH. After heating at reflux for 4.5 hr (odor of NH_3 no longer present), the cooled yellow solution was filtered through a medium porosity sintered funnel and diluted with 900 ml of H_2O. Acidification of the solution with concentrated HCl (*ca.* 13 ml) to pH 2 (pHydrion paper) followed by filtration and drying of the precipitate yielded the crude acid which after recrystallization from EtOH–DMF (4:1.25) afforded 8.3 g of solid, mp 317–320° dec. The analytical sample melted at 324° dec; ir as expected.

8-Chlorobenzo[*h*]-1,6-naphthyridine-4-carboxoyl Chloride (13).—A mixture of 43 ml of freshly distilled $SOCl_2$[18] and 43 g of the acid **12** was heated at reflux for 6 hr. Excess $SOCl_2$ was removed by distillation at reduced pressure and the residue was refluxed with 50 ml of Skellysolve B. The acid chloride (**13**) was filtered under dry N_2 and dried over H_2SO_4 (10 Torr) to yield 4.5 g (96%) of yellow solid; mp 182–188°; ir as expected.

4-(8-Chlorobenzo[*h*]-1,6-naphthyridyl) Diazomethyl Ketone (14).—The washed acid chloride **13** (4.5 g, 0.017 mol) was slowly added to a cold (0 to 10°), well-stirred, solution of CH_2N_2 in Et_2O[19] containing 0.07 mol of CH_2N_2. The reaction mixture was protected from light since the diazomethyl ketone was light sensitive. The mixture was stirred for 1 hr at ice bath temperature and then for 15 min at room temperature. The solid was collected by filtration and pressed dry. Insertion of a sample of this material into the melting point apparatus at temperatures above 187° produced an immediate explosive decomposition; ir as expected (only a very weak signal was observed at 1739, indicative of a small amount of acid chloride[20] contamination in the sample), nmr as expected.

4-(8-Chlorobenzo[*h*]-1,6-naphthyridyl) Bromomethyl Ketone (15).—A solution containing 5.7 g of 48% HBr (0.035 mol) in 4 ml of anhydrous Et_2O was added to a mixture of the crude **14** and 35 ml of CH_2Cl_2 over a 5-min period with stirring and then heated with a 70° water bath, refluxing for 1 hr. The HBr salt of the bromomethyl ketone was filtered and dissolved in 400 ml of DMF to give a dark brown solution. The crude bromomethyl ketone (free base) was precipitated by the addition of 500 ml of cold H_2O to the cooled DMF solution. The solid was filtered, washed thoroughly with 200 ml of H_2O, dried *in vacuo* over H_2SO_4, and washed with 60 ml of anhydrous Et_2O to yield 3.5 g (61%) of **15**, mp 151° dec. The analytical sample (cyclohexane) melted at 154° dec; ir 1692 (C=O); nmr δ 4.60 (s, 2, $COCH_2Br$), 9.48 (d, 1, J = 0.08, aromatic H_2), 7.95 (d, 1, J = 0.08, aromatic H_3), 9.92 (s, 1, aromatic H_5), 9.27 (d of d, 1, J = 0.15, 0.01 aromatic H_{10}), 7.88 (d of d, 1, J = 0.15, 0.04, aromatic H_9), 8.38 (d, 1, J = 0.04, aromatic H_7).

4-(8-Chlorobenzo[*h*]-1,6-naphthyridyl)ethylene Oxide (16).—A mixture of 3.3 g (0.01 mol) of **15**, 50 ml of anhydrous *i*-PrOH, and 2.0 g of freshly distilled $Al(O\text{-}i\text{-}Pr)_3$ was heated by an oil bath while effecting partial take-off of the distillate at a rate of 20 ml/hr. (The distillate, 45 ml total, was tested with 2,4-DNP t.s. for the presence of Me_2CO which was negative after 2.25 hr.) Anhydrous *i*-PrOH was added to the reaction flask as needed during the distillation. The dark brown reaction mixture was concentrated by evaporation with dry N_2. When the mixture became thick, the flask was immersed in an ice bath and 25 ml of H_2O was added. The chunks of solid were broken and stirred into the tan mixture. A cold aqueous solution of 15 g NaOH in 25 ml of H_2O was added and the mixture was stirred for 20 min with cooling and 10 min at room temperature. The tan solid was collected by filtration, washed thoroughly with 100 ml of H_2O, filtered, and dried *in vacuo* (10 Torr) over H_2SO_4 to yield 2.5 g (97%) of the epoxide **16**: immediate charring melt at 194°; ir almost complete loss of 1629 cm^{-1} signal (C=O); nmr δ 4.76



(d of d, 1, J = 0.07, 0.04 C**H**—CH_2), 3.49 (d of d, 1, J = 0.1, 0.04, CH—C), 2.92 (d of d, 1, J = 0.1, 0.07, CH—C),

9.18 (d, 1, J = 0.08, aromatic H_2), 7.58 (d, 1, J = 0.08, aromatic H_3), 9.72 (s, 1, aromatic H_5), 9.15 (d of d, 1, J = 0.14, 0.01, aromatic H_{10}), 7.72 (d of d, 1, J = 0.14, 0.04, aromatic H_9), 8.22 (d, 1, J = 0.04, aromatic H_7).

8-Chloro-4-(2′-*N*,*N*-dibutylamino-1′-hydroxyethyl)benzo[*h*]-1,6-naphthyridine (17).—A mixture of 2.4 g of crude **16**, 7.2 g of dry Bu_2NH, and 3 ml of DMF was stirred and heated by a 100–125° oil bath for 3 hr. The dark brown solution was diluted with 50 ml of H_2O and extracted with five 75-ml portions of Et_2O. The combined Et_2O extract was washed with two 100-ml portions of H_2O and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The dark brown residue solidified upon standing *in vacuo* over H_2SO_4 (2.6 g) and was recrystallized from MeOH–H_2O using decolorized charcoal, yielding 1 g of off-white solid, mp 90–91°; ir 3390 (OH), 2940 (CH), 725 cm^{-1} [$(CH_2)_n$]; nmr δ 5.66 (broad, d of d, 1, J = 0.17, 0.07, C**H**OH), 4.5 (broad, s, O**H**), 2.67 (NCH_2), 1.43 (CCH_2), 0.93 (CCH_3), 9.31 (d, 1, J = 0.08, aromatic H_2), 8.07 (d of d, 1, J = 0.08, 0.01, aromatic H_3), 9.74 (s, 1, aromatic H_5), 9.20 (d of d, 1, J = 0.15, 0.01, aromatic H_{10}), 7.82 (d of d, 1, J = 0.15, 0.04, aromatic H_9), 8.22 (d, 1, J = 0.04, aromatic H_7).

(18) L. F. and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y. 1967, p 1158. Use of impure $SOCl_2$ gives excessive salt formation which interferes with the following CH_2N_2 reaction.

(19) J. DeBoer and H. J. Backer, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y. 1963, p 250.

(20) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden Day, San Francisco, Calif., 1962.